Appendix D.—A Description of Guillain=Barre Syndrome Due to Influenza Vaccine*

Reprinted from Arthur D. Little,
Estimated Economic Costs of Selected Medical Events Known or Suspected To Be Related to the Administration of Common Vaccine,
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Clinical Profile

Etiology

The Guillain-Barre Syndrome (GBS) was first described by Landry in 1859 (l), then by Guillain, Barre, and Strohl in 1919 (2). It is also known as acute postinfectious neuritis, acute ascending paralysis and polyradiculoneuritis. The etiology has not been definitively established, although it has been associated with a variety of viral, bacterial, and other infections, as well as endocrine, hematologic, dermatologic, allergic and neuropsychiatric disorders, various toxins and drugs, and with vaccines for rabies, tetanus, typhoid, pertussis, diptheria, smallpox, polio, and influenza (3).

Clinical Manifestations

Although the clinical presentation is fairly uniform, numerous diagnostic criteria have been proposed without universal acceptance. In addition to the original descriptions, detailed criteria have been outlined by Osler and Sidell (4), Marshall (5), Wiedenholt, et al (6), McFarland and Heller **(7),** Ravn (8) and Masucci and Kurtzke (9). In 50 to 75 percent of nonvaccine-related cases, a history of mild respiratory or gastrointestinal infectious illness, within the preceding 4 weeks, can be elicited. In vaccine associated cases, there is no preceding acute infectious illness in 75 percent of cases (10). There is usually an asymptomatic afebrile period of 1 to 3 weeks, then vague pains or paresthesia of the hands and feet are reported in 75 to 90 percent of cases. The first symptom of prominence is muscle weakness, involving the proximal or distal muscles of the legs, then the arms, but this ascending progression is by no means constant. This involvement is usually bilateral (95 percent) but may be asymmetric. The progression of sensory and other symptoms is gradual and usually complete within 2 weeks, but occasionally can continue for months. Facial weakness and involvement of any or all cranial nerves occur in **50** to 80 percent of cases. Cranial nerves are more often involved in vaccine-associated cases (10). Urinary incontinence or retention may occur in 20 percent but is transient. From 10 to 25 percent of patients may have paralysis of breathing and require artificial respiratory support. Pulmonary complications, anoxia and seizures, and residual neurological deficits may occur, but complete recovery is gradually achieved in one year. Mortality, usually from respiratory involvement, is approximately 5 percent. Residual paralysis occurs in 10 to **30** percent of cases.

Physical examination is marked by bilateral motor weakness of the lower extremities, upper extremities, and trunk. Muscle atrophy and fasciculations may be noted. Sensory deficits may involve position, vibration pain, and light touch. Deep tendon reflexes are depressed or absent; superficial reflexes may be absent, but are usually intact. As noted, cranial nerves may be involved, and papilledema may be found. Some patients, especially children, may have neck stiffness as a sign of meningeal irritation (11). Autonomic dysfunction with hypertension, postural hypotension, facial flushing, and tachycardia may occur.

Laboratory abnormalities are few, but CSF findings are diagnostic. CSF protein should be elevated (above 60 mg/dl), but may be within normal limits early in the illness. The CSF cell count is usually less than **20** WBC/cmm. Peripheral white blood cell count, differential, and erythrocyte sedimentation rates are usually normal. Serum calcium may be elevated in patients immobilized for prolonged periods and electrolyte imbalances with inappropriate secretion of antidiuretic hormone have been reported. Electromyography is usually diagnostic (fasciculations), and motor nerve conduction is delayed.

Epidemiology

In February 1976, an influenza virus was isolated during an epidemic at Fort Dix, N. J., antigenically similar to the virus implicated in the 1918 influenza pandemic. The Federal Government then initiated a

● NOTE: Reference citations for app. D refer to the list of references at the end of app. D.

project to immunize much of the population of the United States. Between October 1, 1976, and December 16, 1976, nearly 43 million doses of killed influenza A/New Jersey/1976 vaccine were administered. The program was abruptly halted when an increasing number of reports of GBS (associated with vaccine inoculation) were reported. By January 10, **1977,** a total of **581** cases of GBS had been reported, of which **295** had received the vaccine. 11 percent of the patients who received vaccine were less than 3 years of age. Fifty-eight percent were between 30 and 59 years, and 31 percent were 60 years or older. Of 266 unvaccinated patients, 4 percent were less than 30 years, 39 percent between 30 and 59, and 17 percent were 60 or older. There was no differences between sexes. Cases were noted in 49 of 50 States (12).

The clinical states of vaccinated and non-vaccinated patients as reported by the Center for Disease Control were remarkably similar, significantly differing only in history of previous acute **(27 v. 62** percent) or chronic illness (44 v. 27 percent), involvement of cranial *nerves* (64 v. 47 percent), and sensory symptoms (87 v. 74 percent). Of the vaccinated patients, there were 41 percent with respiratory involvement, **23** percent placed on a respirator and 5 percent of 299 cases died. Within 8 to 28 days following vaccination, **75.2** percent had onset of paralysis, 3.3 percent within 7 days after vaccination, and 21.5 percent more than **28** days following vaccination (lo).

The relative risks of GBS in influenza vaccinated persons was approximately 12 times greater than in unvaccinated persons (10). The risk was similar for monovalent or bivalent vaccine. Age-specific attack rates per million population per month were *2.48* for vaccinated v. 0.34 for unvaccinated in ages O to 17 years, 3,45 and 0.70 for ages 18 to 24, 9.21 and 0.56 for ages 25 to 44, 6.49 and 0.81 for ages 45 to 64, 7.22 and 0.76 for over 65, and 6.99 and 0.58 for all ages. Thus, all ages were at risk.

Pathology

Pathological examination varies with the stage of disease progression. There are no significant pathologic changes in the cerebrum, brain stem, or spinal cord, except for severe changes in the anterior horn cells and motor nuclei of the brain stem. Acutely, there is marked edema of the spinal roots and cranial nerves. Later, demyelination and degeneration of the spinal and cranial nerve axons are *seen.* Lymphocytic inflammatory cells invade the myelin sheath and Schwann cell proliferation follows. Chromatolysis of dorsal root ganglia and anterior horn cells may be observed (13).

Diagnosis

Diagnostic criteria are those outlined under clinical manifestations and include:

1. acute *or* subacute onset of muscle weakness and/or sensory symptoms (i. e., paresthesia, numbness or pain);
2. usually ascending spread (may be descending, or variable) with progression over 1 to 2 weeks (up to 2 months);
3. bilateral (may be asymmetric) muscle involvement;
4. deep tendon reflexes absent or diminished;
5. cranial nerves may be involved; and
6. CSF protein elevated (>60 mg/dl), CSF WBC count < 20/cmm.

Differential Diagnosis

The differential diagnosis of influenza-vaccine-associated GBS includes:

1. *GBS secondary to other* causes, including viral infections (infectious mononucleosis, measles, hepatitis, upper respiratory and gastrointestinal infections, etc.), bacterial infections (strep tococcal, etc.), other vaccinations, (rabies, tetanus toxoid, etc.), autoimmune disorders (lupus erythematosis, polyarteritis nodosa, etc.) malignant diseases (Hodgkin's disease, etc.), endocrine disorders (diabetes mellitus, etc.), poisons and toxins and antibiotic therapy (penicillin, etc.). Only a complete history, appropriate viral cultures and serologies, toxic screens, and search for underlying disease can implicate these disease etiologies.
2. *Poliomyelitis,* which is differentiated by epidemic occurrence, meningeal symptoms, biphasic course (aseptic meningitis then paralysis), fever, asymmetric muscle involvement, CSF pleocytosis without cytoalbumin dissociation and positive viral cultures.
3. *Acute myelitis,* which is marked by sensorimotor paralysis below a specific spinal level.
4. *Diphtheric polyneuropathy* characterized by weakness or paralysis of limbs and muscles innervated by cranial nerves associated with loss of position and vibratory sensation. This can be easily diagnosed by the obvious symptoms of laryngeal, pharyngeal or nasal diptheria, i.e., fever, pseudomembrane, proteinuria and positive culture for Corynebacteria diptheriae.
5. *Porphyric polyneuropathy,* a rapidly advancing severe, symmetric polyneuropathy with or without psychosis or convulsions. Diagnosis of underlying porphyria is accomplished by usual serum and/or urine tests.

Outcomes

Few prognostic data are available regarding influenza vaccine associated cases of GBS. Prognosis of other **cases** is usually good. Death occurs in approximately 5 percent of cases (5,6,10,14).

In vaccine associated cases, 3 to 4 extremities are involved in 85 percent of cases, cranial nerves in 47 percent, respiratory impairment occurs in 41 percent, and ventilator assistance is required in 25 percent (10).

The duration of hospitalization ranges from weeks to years depending upon the eventual outcome. Of 97 patients from the Mayo Clinic (6), 50 made complete recovery with a year, 7 more in 2 years, and 4 more after 2 years. Twelve patients made incomplete recovery, five had moderate incapacity, four marked incapacity, and three respiratory insufficiency. Fifteen patients were improved when last seen, four unchanged 3 or more years after diagnosis, and five dead. From Columbia Presbyterian Medical Center, 49 of 81 patients were reexamined at least 2 years after onset of GBS. Of these, 8 had marked distal weakness, and 8 mild distal weakness (14).

Impairment may range from mild weakness of one or more extremities to marked paralysis and respiratory insufficiency requiring ventilator assistance, and constant nursing care. Relapses may occur weeks or years after resolution' of symptoms (14,15). Influenza vaccination of persons who have previously suffered from GBS may precipitate a second attack (16). From 50 to 60 perceni of patients should be able to return to their normal routine within 1 year of onset. Approximately 15 percent will be completely disabled (6,14).

Appendix D References

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